PATENT
2815-0127P

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT:	JENTSCH, Thomas J.	CONF:	9782
SERIAL NO.:	09/492,361	GROUP:	1646
FILED:	January 27, 2002	EXAMINER:	Murphy, J.
FOR:	POTASSIUM CHANNELS AND GENES ENCODING THESE POTASSIUM CHANNELS		

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Dr. Bo Skaaning Jensen of the Ion Channel Target Discovery Department, NeuroSearch A/S, Denmark, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am the Head of Ion Channel Target Discovery and conducted the experiments described below.

I am familiar with the above referenced patent application, as well as the development, usages and properties of potassium channels and the genes that encode them.

I have read and understand the subject matter of the Office Action of February 22, 2002.

The following comments are offered in support of the patentability of the instant invention.

I have made a direct comparison of the nucleotide sequences that encode KCNQ4 (identified as SEQ ID NO: 1 in the application) and KCNQ2, identified by Singh et al. and appearing in GenBank under the accession number AF033348. The GenBank description is enclosed.

Using the Blast 2 sequences program provided by the National Center for Biotechnology Information (NCBI), I have aligned the coding sequences (CDS) of the two sequences. The report generated is enclosed. As shown in the report, there is no significant identity when determined over the entire sequence. Only for four partial (internal) sequences the program was able to detect any significant identity. This result can be represented in the following way:

Fraction 1: Determined over 814 bases, 76% identity

Fraction2: Determined over 147 bases, 84% identity

Fraction 3: Determined over 64 bases, 82% identity

Fraction 4: Determined over 48 bases, 85% identity

Of a total sequence of 2088 nucleotides of KCNQ4, only 1073 bases (814+147+64+48) could be blasted, which corresponds to only 51.4% of the CDS. Overall this leaves an identity of less than 50% between the nucleotide sequence encoding the KCNQ4 channel of the invention and that of the KCNQ2 channel of Singh et al. So pending claim 2, which claims at least 90% homology, is definitely not anticipated by the disclosure of Singh et al.

Concerning pending claim 1, which is directed to hybridization conditions, there is no strict correlation between homology and hybridization conditions. However, as claim 1 is directed to high stringency conditions, and in view of the low percent identity determined above, the skilled person will realize that the KCNQ4 sequence of the invention will not hybridize with the KCNQ2 sequence of Singh *et al.*

What exactly is the homology of the sequences that are capable of hybridizing under these circumstances depends on the particular sequences in question and can only be determined experimentally (see, e.g., "Current protocols in Molecular Biology" (Ausubel et al, eds); John Wiley & Sons, Inc. 1998, Vol. 1, comments to Section 6.3.5: "*High-stringency wash is determined empirically. The relative homology between the probe and target sequence is a determining parameter. If the homology is 100%, a high temperature (65° to 75°C) can be used. As the homology drops, lower washing temperatures must be used.*" Therefore it is fair to expect a homology in the order of 80-100%.

To summarize, because of the lack of significant identity between the nucleic acid sequences encoding the KCNQ4 and KCNQ2 channels and in view of the stringency associated with the wash conditions, no hybridization between the KCNQ4 nucleic acid sequence and that of KCNQ2 would occur.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: JUNE 26 2002

Dr. Bo Skaaning Jensen

Enclosures: As stated above

Curriculum Vitae Bo Skaaning Jensen, Ph.D.

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Personal

Born May 6th, 1965, Gentofte
Citizenship: Danish
Marital status: Married, 2 children
(Anders, January 13th 1991; Lasse, November 27th 1993)

Summary

A highly entrepreneurial and innovative scientist with 6 years of experience in a leading Danish biotech company. Proven track record in project and department management as well as in business development.

Business Experience

1. January 2000 - present

Head of Department, Ion Channel Molecular Biology, NeuroSearch A/S
NeuroSearch is a leading Danish biopharmaceutical company committed to the discovery and development of new drugs mainly for the treatment of diseases of the Central Nervous System.

Major Achievements: In the Board of Directors, Poseidon Pharmaceutical, November 1st, 2001. Participated in preparation of the investor presentation and business plan for Poseidon Pharmaceutical, a novel 100% Neurosearch-owned company. In the Board of Directors, Azign Bioscience, from March 23rd, 2001. Participates in drafting the investor presentation and business plan for Azign Bioscience, a 100% Neurosearch-owned company. Participated in the first drafts of the investor presentation and business plan for Sophion Bioscience, a Neurosearch spin-out company. Project manager for the Research programme on SK/IK channel Modulators. Program manager for a research program on KCNQ channel Modulators. Wrote both scientific non-confidential as well as confidential material for these programmes to be used in marketing the programmes. Prepared the scientific project presentation of the programmes.

1. April 1997 – 1. January 2000

Senior Research Scientist, Electrophysiology, NeuroSearch A/S

Major Achievements: Project manager for two Research programmes on IK channel Modulators. Negotiated together with Mette Kirstine Agger the Research collaboration Agreement with Pharmexa (previously M&E Biotech) and drafted the research plan for the collaboration together with Vice President Anand Gautam of Pharmexa. Program manager for a research program on KCNQ channel Modulators. Wrote both non-confidential as well as confidential material for all three programmes to be used in marketing the programmes. Prepared the project presentation of all three programmes.

15. December 1996 – 31. March 1997

Research Scientist, Molecular Screening, NeuroSearch A/S

1. July 1994 - 15. December 1996

Post Doc at the Dept. Chem. Immunol, Weizmann Institute of Science, Israel/August Krogh Institute, University of Copenhagen

Scientific Experience

Education: 1991, Master in Biology, University of Copenhagen
1994, Ph.D. in Cell Physiology and Biological Chemistry, University of Copenhagen

Publications:

A. In "peer review" journals:	23
B. Contributions to Proceedings:	4
C. Published abstracts:	18
D. Patent applications:	11
E. Reviews	3 (invited, 2 in press)
F. Scientific Articles in newspapers	1
G. Theses	2

Scientific Prizes: 1. Prize in lecturing at the Winter Meeting in the Danish Society for Toxicology and Pharmacology, January 28th 1998

Other Professional Activities: Member of:
The Danish Weizmann Society (at present Secretary in the Society)
The Danish Biological Society
The European Oocyte Club
Danish Society of Toxicology and Pharmacology
Society of General Physiology
American Society of Physiology

Organizer of:
The Danish-Israeli Binational Symposia on Neuroscience (from 1999)
The Sandbjerg Meetings on Membrane Transport (from 2000)

Referee for: *Journal of Biological Chemistry; Cellular and Molecular Biology Letters*
(for papers on K^+ channels)

Conferences and Congresses (only oral presentations):

Invited presentations:
24. August, 1997. XVth Scandinavian Workshop on In Vitro Toxicology
Roskilde Universitetscenter, Roskilde
28. January 1998. Danish Society for Toxicology and Pharmacology
Winter meeting, Odense Universitetshospital, Odense
XX. -YY. May 2000. 33. Sandbjerg Conference on
Membrane Transport, Sønderborg.
21. September 2000. Medicon Valley BioConference, Lund, Sweden.
9.-12. February, 2002. The 6th International Symposium on
predictive oncology & intervention strategies, Paris, France

Publications

A: Publicationer in "peer review" journals

A1 B.S. Jensen, F. Jessen, & E.K. Hoffmann, 1993. "Na^+,K^+,Cl- cotransport and its regulation in Ehrlich ascites tumor cells. Ca^{2+}/calmodulin and protein kinase C dependent pathways." *J. Membrane Biol.* **131**, 161-178.

A2 B.S. Jensen, F. Jessen, B. Kramhøft, I.H. Lambert & E.K. Hoffmann. 1993. "$HgCl_2$ activates cation and anion transport systems in Ehrlich ascites tumor cells." *Cell. Physiol. Biochem.* **3**, 97-110.

A3 A.K. Larsen, B.S. Jensen & E.K. Hoffmann. 1994. "Protein Kinase C activity during Cell Volume Regulation in Ehrlich mouse ascites tumor cells" *Biochim. Biophys. Acta* **1222**, 477-482.

A4 A. Bækgaard, B.S. Jensen & E.K. Hoffmann. 1995. "Antibodies against proteins of the Na/K/Cl cotransporter inhibit volume regulation and bumetanide sensitive K^+ fluxes." *Cell. Physiol. Biochem.* **5**, 107-117.

A5 S.G. Kachalsky, B.S. Jensen, D. Barchan & S. Fuchs. 1995. "Two subsites in the binding domain of the acetylcholine receptor: An aromatic subsite and a proline subsite" *Proc. Natl. Acad. Sci. USA* **92**, 10801-10805.

A6 T. Krarup, B.S. Jensen & E.K. Hoffmann. 1996. "Occlusion of Rb in the Na^+,K^+,$2Cl^-$ cotranspc ..r of Ehrlich ascites tumor cells" *Biochim. Biophys. Acta* **1284**, 97-108

A7 B.S. Jensen & E.K. Hoffmann. 1997. "Hypertonicity enhances expression of functional Na^+,K^+,$2Cl^-$ cotransporters in Ehrlich ascites tumour cells" *Biochim. Biophys. Acta* **1329**, 1-6

A8 B.Skaaning Jensen, B. Levavi-Sivan, C.S. Fishburn & S. Fuchs. 1997. "Functional expression of the murine D_2, D_3 and D_4 dopamine receptors in *Xenopus laevis* oocytes" *FEBS Lett.***420**, 191-195

A9 O. Asher, B.S. Jensen , M. Lupu-Meiri, Y. Oron, S.Fuchs.1998 "The mongoose acetylcholine receptor alpha-subunit: analysis of glycosylation and alpha-bungarotoxin binding." *FEBS Lett.* **426(2)**:212-6.

A10 T. Krarup, L.D. Jakobsen, B.S. Jensen, E.K. Hoffmann. 1998 "Na^+-K^+-$2Cl^-$ cotransport in Ehrlich cells: regulation by protein phosphatases and kinases." *Am J Physiol.*;**275(1 Pt 1)**:C239-50.

A11 O.Asher, M. Lupu-Meiri, B.S. Jensen, T. Paperna, S. Fuchs, Y. Oron. 1998. "Functional characterization of mongoose nicotinic acetylcholine receptor alpha-subunit: resistance to alpha-bungarotoxin and high sensitivity to acetylcholine." *FEBS Lett*; **431(3)**: 411-4.

A12 B.S. Jensen, D. Strøbæk, P. Christophersen, T.D. Jørgensen, C. Hansen, A. Silahtaroglu, S.P. Olesen, P.K. Ahring. 1998. "Characterization of the cloned human intermediate-conductance Ca^{2+}-activated K^+ channel" *Am J Physiol*; **275(3 Pt 1)**:C848-56.

A13 K.A. Pedersen, R.L. Schrøder, B. Skaaning-Jensen, D. Strøbæk, S.P. Olesen, P. Christophersen. 1999. "Activation of the human intermediate-conductance Ca^{2+}-activated K^+ channel by 1-ethyl-2-benzimidazolinone is strongly Ca^{2+}-dependent." *Biochim Biophys Acta*; **1420(1-2)**:231-40.

A14 B.S. Jensen, N. Ødum, N.K Jørgensen, P. Christophersen, S.-P. Olesen. 1999. "Inhibition of T cell proliferation by selective block of Ca^{2+}-activated K^+ channels." *Proc Natl Acad Sci U S A*; **96** (**19**): 10917-21.

A15 K.A. Pedersen, N.K. Jørgensen, B.S. Jensen, S.-P. Olesen. 2000. "Inhibition of the human intermediate-conductance, Ca^{2+}-activated K^+ channel by intracellular acidification" *Pflugers Arch*; **440(1)**:153-6.

A16 R.L. Schrøder, B.S. Jensen, D. Strøbæk, S.-P. Olesen, P. Christophersen. 2000. "Activation of the human, intermediate-conductance, Ca^{2+}-activated K^+ channel by methylxanthines" *Pflugers Arch*; **440(6)**:809-18.

A17 M. Grunnet, B.S. Jensen, S.-P. Olesen, D. Klærke. 2001. "Apamin interacts with all subtypes of cloned small-conductance Ca^{2+}-activated K^+ channels." *Pflüger's Archiev (Eur J Physiol)* **441(4)**:544-50.

A18 R. Søgaard, T. Ljungstrøm, K.A. Pedersen, S.-P. Olesen, B.S. Jensen. 2001. "KCNQ4 channels expressed in mammalian cells: Functional characteristics and pharmacology." *Am. J. Physiol. (Cell Physiol.)* **280(4)**:C859-66.

A19 Y.V. Korolkova, S.A. Kozlov, A.V. Lipkin, K.A. Pluzhnikov, J.K. Hadley, A.K. Filippov, D. A. Brown, K. Angelo, D. Strøbæk, T. Jespersen, S.-P. Olesen, B.S. Jensen, E.V. Grishin. 2001. "An ERG channel inhibitor from the scorpion *Buthus eupeus*." *J. Biol. Chem.* 276 (13), p. 9868.

A20 M. Grunnet, T. Jespersen, K. Angelo, C. Frokjaer-Jensen, D.A. Klaerke,S.-P. Olesen, B.S. Jensen. 2001. "Pharmacological modulation of SK3 channels" *Neuropharmacology*, **40 (7)**: 879-887.

A21 R.L. Schroder, T. Jespersen, P. Christophersen, D. Strobaek, B.S. Jensen,S.-P. Olesen. 2001. "KCNQ4 channel activation by BMS-204352 and retigabine" *Neuropharmacology*, **40 (7)**: 888-898.

A22 D.S. Dupuis, R.L. Schroder, T. Jespersen, J.K. Christensen, P. Christophersen, B.S. Jensen, S.P. Olesen. 2002. "Activation of KCNQ5 channels stably expressed in HEK293 cells by BMS-204352." *Eur J Pharmacol.*: **437(3)**: 129-37.

A23 M.Grunnet, N. MacAulay, N. K. Jorgensen, B.S. Jensen, S.-P. Olesen and D.A. Klaerke. 2002. "Regulation of cloned, Ca^{2+}-activated K^+ channels by cell volume changes" *Pflügers Arch - Eur J Physiol.*, **444**: 167-177

B: Publications in proceedings

B1 S. Fuchs, D. Neumann, D. Barchan, S. G.Kachalsky, B. Jensen & M. Balass. 1996. "Mapping of functional sites at the nicotinic acetylcholine receptor" *Perspectives in Neuroscience Research*, 57-75. C.K.Tan, E.A. Ling, C.B.C. Tan. *Editors*. Singapore.

B2 Asher O, Lupu-Meiri M, Jensen BS, Paperna T, Oron Y, Fuchs S. 1998 "How does the mongoose cope with alpha-bungarotoxin? Analysis of the mongoose muscle AChR alpha-subunit" *Ann N Y Acad Sci*; **841**:97-100.

B3 Jorgensen TD, Jensen BS, Strobaek D, Christophersen P, Olesen SP, Ahring PK. 1999. "Functional characterization of a cloned human intermediate-conductance Ca(2+)-activated K+ channel." *Ann N Y Acad Sci*; **868**:423-6.

B4 B.S. Jensen, T.D. Jørgensen & S.P. Olesen. 1999. "A Method of screening for G-protein linked receptor acrivation." *Research Disclosure*. 42625; 1301-1302

C: Publiced Abstracts

C1 B.S. Jensen & E.K. Hoffmann. 1990. On the K^+ dependence of the cation/anion cotransport system in Ehrlich ascites tumor cells. *Acta Physiol. Scand.* **140** (1), 34A.

C2 A. Bækgaard, B.S. Jensen, F. Jessen & E.K. Hoffmann. 1991. Antibodies against proteins of the Na/K/Cl cotransporter inhibit volume regulation and bumetanide sensitive K^+ fluxes. *Acta Physiol. Scand.* **143** (1), 28A.

C3 B.S. Jensen, F. Jessen & E.K. Hoffmann. 1992. Activation of Na^+,K^+,Cl^- cotransporter in Ehrlich ascites tumor cells. *Acta Physiol. Scand.* **146** suppl. 608, 3.48.

C4 H. Harbak, B.S. Jensen, E.K. Hoffmann & L.O. Hoffmann. 1992. Concurrent inhibition of the KCl loss and cell shrinkage and of Na^+,K^+,Cl^- cotransport induced by Ca^{2+}-mobilizing agonists in the Ehrlich mouse ascites tumor cell. *Acta Physiol. Scand.* **146** suppl. 608, 3.58.

C5 L.D. Jakobsen, B.S. Jensen & E.K. Hoffmann. 1994. Regulation of the $Na^+/K^+/2Cl^-$ cotransporter in Ehrlich ascites tunour cells. *Acta Physiol. Scand.* **151** (4), 27A.

C6 T. Krarup, B.S. Jensen, & E.K. Hoffmann. 1994. Occlusion of Rb in the Na^+,K^+,$2Cl^-$ cotransport system of Ehrlich ascites tumor cells. *Acta Physiol. Scand.* **151** (4), 28A.

C7 B.S. Jensen, D. Strøbæk, P. Christophersen, T.D. Jørgensen, S.-P. Olesen & P.K. Ahring. 1998. A novel human Ca^{2+}-activated K^+ channel with intermediate-conductance. Molecular cloning, chromosomal localization and functional expression. *Biophys. J.* **74** (2 part 2), A43.

C8 S. Fuchs, O.Asher, S. Ariel, D. Barchan, B.S. Jensen, S.G. Kachalsky, T. Paperna, M. Lupu-Meiri, & Y. Oron. 1997. The Nicotinic acetylcholine receptor of the mongoose; tricks of evolution. *Neurosience Lett.* **Suppl. 48**; S17

C9 S.G. Kachalsky, B.S. Jensen, D. Barchan & S. Fuchs. 1997. Differential recognition of alpha-Bungarotoxin and of the site-specific monoclonal antibody 5.5 by the nicotinic acetylcholine receptor. *Neurosience Lett.* **Suppl. 48**; S18

C10 K.A. Pedersen, R.L. Schrøder, B.S. Jensen, S.P. Olesen & P. Christophersen. 1999. Activation of the cloned hIK channel by 1-ethyl-2-benzimidazolone is calcium-dependent. *Biophys. J.* **76 (1 part 2)**; A330

C11 K.A. Pedersen, N.K. Jørgensen, B.S. Jensen & S.P. Olesen. 1999. Inhibition of the Ca^{2+}-activated, intermediate-conductance K^+ channel from intracellular acidification. *The Physiologist* **42 (4)**; A-7

C12 R.L. Schrøder, P. Christophersen, S.P. Olesen, D. Strøbæk, K.A. Pedersen & B.S. Jensen. 1999. Effects of methylxanthines on the human Ca^{2+}-activated, intermediate-conductance K^+ channel (hIK). *The Physiologist* **42 (4)**; A-7

C13 M. Grunnet, S.-P. Olesen, B.S. Jensen & D. A. Klærke. 1999. Small-conductance Ca^{2+}-activated K^+ channels show differential sensitivity to apamin. *The Physiologist* **42 (4)**; A-8

C14 R. Søgaard, T. Ljungstrøm, K.A. Pedersen, B.S. Jensen & S.-P. Olesen. 1999. Stable expression and pharmacological characterization of the KCNQ4 channel. *The Physiologist* **42 (4)**; A-20

C15 B. S. Jensen, N. Ødum, N.K. Jørgensen, P. Christophersen & S.P. Olesen. 1999. Inhibition of T cell proliferation by selective block of calcium-activated K^+ channels. *The Physiologist* **42 (4)**; A-21

C16 Dan A Klaerke, Nanna MacAulay, Bo S Jensen, Søren P Olesen, Tina Skafte, Morten Grunnet. 2001. CELL VOLUME CHANGES SPECIFICALLY REGULATE CERTAIN CATION CHANNELS. *Biophys. J.* **80 (2 part 2)**, 506A.

C17 Rikke Louise Schroeder, Søren- Peter Olesen, Bo Skaaning Jensen. 2001. BMS-204352 ENHANCES THE KCNQ4 CURRENT. *Biophys. J.* 80 (2 part 2), 211A.

C18 Thomas Jespersen, Kamilla A Pedersen, Dan A Klaerke, Soren P Olesen, Bo S Jensen, Morten Grunnet. 2001. PHARMACOLOGICAL CHARACTERIZATION OF SK3 POTASSIUM CHANNELS STABLY EXPRESSED IN HEK293 CELLS. *Biophys. J.* **80 (2 part 2)**, 214A.

D: Patent applications

D1 B.S. Jensen, D. Strøbæk, P. Christophersen, T.D. Jørgensen & S.-P. Olesen, **IKca Channel Blocking Compounds/Immunosuppressiva**. International Patent Publication No. WO 99/25347.

D2 B.S. Jensen, D. Strøbæk, P. Christophersen, T.D. Jørgensen & S.-P. Olesen, **SKca Channel Blockers**. International Patent Publication No. WO 00/01676.

D3 B.S. Jensen, T. D. Jørgensen, P. K. Ahring, L. Teuber, D. Strøbæk, P. Christophersen & S.-P. Olesen. **IK/SK Channel Opening Compounds**. 1998. International Patent Publication No. WO 00/33834.

D4 B.S. Jensen, P. Christophersen, D. Strøbæk & L. Teuber. 1998. **Novel oxime derivatives for use as SK/IK modulating compounds**. International Patent Publication No. WO 00/34228.

D5 L. Teuber, P. Christophersen, D. Strøbæk & B.S. Jensen. 1998. **Novel isatin derivatives for use as SK/IK modulating compounds**. International Patent Publication No. WO 00/34248.

D6 B.S. Jensen, L. Teuber, P. Christophersen, D. Strøbæk. 1998. **Novel compounds for use as SK/IK/BK modulating compounds**. International Patent Publication No. WO 00/37422

D7 B.S. Jensen, S.-P. Olesen & P. Christophersen. **Triaryl methane compounds for immune-suppression** Filed: 1999. International Patent Publication No. WO 00/69439

D8 B.S. Jensen, L. Teuber, P. Christophersen, D. Strøbæk, S.-P. Olesen. **Novel benzothiazole derivatives for use as SK/IK modulating compounds**. Filed: 1999 International Patent Publication No. WO 00/69838

D9 B.S. Jensen, L. Teuber, D. Strøbæk, P. Christophersen, S.-P. Olesen. **Novel derivatives for use as SK/IK modulating compounds**. Filed: 1999 International Patent Publication No. WO 00/69823

D10 B.S. Jensen, L. Teuber, D. Strøbæk, P. Christophersen. **Novel IK/SK modulating agents.** Filed: 1999 International Patent Publication No. WO 00/69794

D11 B.S. Jensen, R. Schrøder, D. Strøbæk, P. Christophersen.. **Compounds for modulation of KCNQ channels. Filed: 2000**

E: Reviews

E1 Jensen BS, Strøbæk D, Olesen SP, Christophersen P. "The Ca^{2+}-activated K^+ channel of intermediate conductance: a molecular target for novel treatments?"
Current Drug Targets. 2001; 2(4):401-22.

E2 Jensen BS. " BMS-204352: a potassium channel opener developed for the treatment of stroke"
CNS Drug Reviews (in press)

E3 Jensen BS, Madsen LS, Hertz M, Christophersen P "The human intermediate-conductance, Ca^{2+} activated K^+ channel as a therapeutic target" *Expert Opinion on Therapeutic Targets (In press)*

F: Scientific articles in newspapers

F1 Bo Skaaning Jensen. 1998. "Molekyle-trick redder Rikki-Tikki-Tavi" Berlingske Tidende, 4. sektion (Univers), p. 16. (Tuesday August 18th, 1998).

G: Theses

Master Thesis 1991. "Cl^- dependent cotransport and it's regulation in Ehrlich ascites tumor cells"

Ph.D. Thesis. 1994. "Structure, function and regulation of the Na/K/2Cl cotransporter from Ehrlich ascites tumor cells"